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(來函請敍明此檔案號碼) DH DO DIMC/7-30/1
(IN REPLY PLEASE QUOTE THIS FILE REF.)

21 Jun 2022

Dear Healthcare Professionals,

Metformin and reduced vitamin B12 levels: new advice for monitoring patients at risk

Your attention is drawn to the United Kingdom Medicines and Healthcare products Regulatory Agency's (MHRA) announcement that decreased vitamin B12 levels, or vitamin B12 deficiency, is now considered to be a common side effect in patients on metformin treatment, especially in those receiving a higher dose or longer treatment duration and in those with existing risk factors.

Patients with a vitamin B12 deficiency can be asymptomatic or they can present with symptoms of megaloblastic anaemia or neuropathy or both. Other symptoms of low vitamin B12 levels may include mental disturbance (depression, irritability, cognitive impairment), glossitis (swollen and inflamed tongue), mouth ulcers, and visual and motor disturbances. It is important for patients with anaemia or neuropathy caused by vitamin B12 deficiency to be diagnosed and treated as soon as possible to avoid the development of permanent symptoms.

Decreased vitamin B12 levels is a known consequence of long-term treatment with metformin. The mechanism is currently thought to be multifactorial, comprising altered intestinal motility, bacterial overgrowth, and reduced uptake of vitamin B12 within the small intestine (or a combination of these factors).

The known adverse drug reaction of vitamin B12 deficiency was recently reviewed for the brand leader Glucophage (metformin) within Europe with input from the MHRA. After this review, MHRA has agreed that the product information for medicines containing metformin should be updated. The current literature suggest that the frequency of this adverse drug reaction is higher than previously thought. The Glucophage product information for healthcare professionals and patients has now been updated to state that vitamin B12 deficiency is a common adverse drug reaction, and may affect up to 1 in 10 people who take it. The product information has also been updated to note that the risk of this adverse reaction

occurring increases with increasing metformin dose and treatment duration and in patients with risk factors known to cause vitamin B12 deficiency. The updated product information also includes new advice to healthcare professionals to test vitamin B12 levels in those presenting with anaemia or neuropathy and that periodic vitamin B12 monitoring should be considered in patients with risk factors for vitamin B12 deficiency. The product information for other medicines containing metformin will also be updated including fixed-dose combination products containing metformin.

Risk factors for vitamin B12 deficiency are wide ranging. They include: baseline vitamin B12 levels at the lower end of the normal range; conditions associated with reduced vitamin B12 absorption (such as elderly people and those with gastrointestinal disorders such as total or partial gastrectomy, Crohn's disease and other bowel inflammatory disorders, or autoimmune conditions); diets with reduced sources of vitamin B12 (such as strict vegan and some vegetarian diets); concomitant medication known to impair vitamin B12 absorption (including proton pump inhibitors or colchicine); genetic predisposition to vitamin B12 deficiency, such as intrinsic factor receptor deficiency (Imerslund-Gräsbeck syndrome) and transcobalamin II deficiency.

Advice for healthcare professionals:

- Metformin can commonly reduce vitamin B12 levels in patients, which may lead to vitamin B12 deficiency.
- The risk of low vitamin B12 levels increases with higher metformin dose, longer treatment duration, and in patients with risk factors for vitamin B12 deficiency.
- Test vitamin B12 serum levels if deficiency is suspected (for example, in patients presenting with megaloblastic anaemia or new-onset neuropathy) and follow current clinical guidelines on investigation and management of vitamin B12 deficiency.
- Consider periodic vitamin B12 monitoring in patients with risk factors for vitamin B12 deficiency.
- Administer corrective treatment for vitamin B12 deficiency in line with current clinical guidelines; continue metformin therapy for as long as it is tolerated and not contraindicated.

Please refer to the following website in MHRA for details:
https://www.gov.uk/drug-safety-update/metformin-and-reduced-vitamin-b12-levels-new-advice-for-monitoring-patients-at-risk

In Hong Kong, there are 118 registered pharmaceutical products containing metformin. All products are prescription-only medicines. So far, the Department of Health (DH) has received 19 cases of adverse drug reaction related to metformin, but these cases were not related to vitamin B12 deficiency. In light of the above MHRA's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Please note that this letter serves as a means for the DH to communicate important new safety information about registered pharmaceutical products with healthcare professionals in Hong Kong and is not intended to serve as guidelines or to replace professional clinical judgement. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Adverse Drug Reaction Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

(Terence MAN)
for Assistant Director (Drug)